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France

PATENT OF INVENTION

STREPTOGRAMIN DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

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ABSTRACT

Group B streptogramin derivatives of general formula (I) in which R represents a hydrogen atom or an alkyl radical of structure R'-CH_2-(R' being a straight or branched alkyl) or an acyl radical optionally substituted with hydroxyl, R_1 and R_2, which are identical or different, represent a hydrogen atom or an alkyl radical,

Ra is an Me or Et radical, and Rb, Rc and Rd are defined below:

1) Rb and Rc are H and Rd is H or an MeNH or NMe2 radical,
2) Rb is H, Rc is H, Cl or Br, or alkenyl (3 to 5C) and Rd is -NMe-R''', R''' being alkyl, hydroxyalkyl (2 to 4C) or alkenyl (2 to 8C), phenylalkenyl, cycloalkyl(3 to 6C)methyl, benzyl, substituted benzyl, heterocyclylmethyl, heterocyclylethyl, or R''' is -CH_2CN, -CH_2COOH or -CORe or -CH_2CORe for which either Re is -OR'e, or Re is alkylamino,

alkylmethylamino, heterocyclylamino or heterocyclylmethylamino,

3) Rb is H, Rd is a radical $-NHCH_3$ or $-N(CH_3)_2$ and Rc is Cl or Br, or alkenyl (3 to 5C), [if Rd is $-N(CH_3)_2$],

4) Rb and Rd are H and Rc is halogen, or alkylamino or dialkylamino, alkyloxy, trifluoromethoxy, thioalkyl, alkyl (1 to 6C) or trihalomethyl,

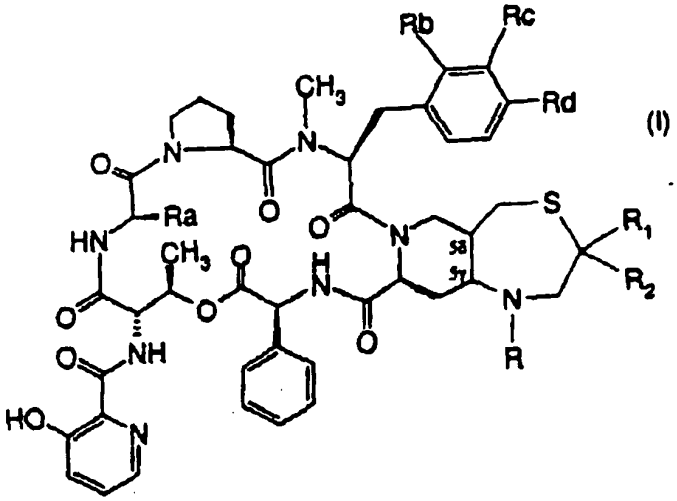
5) Rb and Rc are H and Rd is halogen, or ethylamino, diethylamino or methylethylamino, alkyloxy or trifluoromethoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl(1 to 6C), phenyl or trihalomethyl,

6) Rb is H and Rc is halogen or alkylamino or dialkylamino, alkyloxy or trifluoromethoxy, thioalkyl, alkyl (1 to 3C), and Rd is halogen or an amino, alkylamino or dialkylamino, alkyloxy or trifluoromethoxy, thioalkyl, alkyl(1 to 6C) or trihalomethyl radical

7) Rc is H and Rb and Rd are CH_3

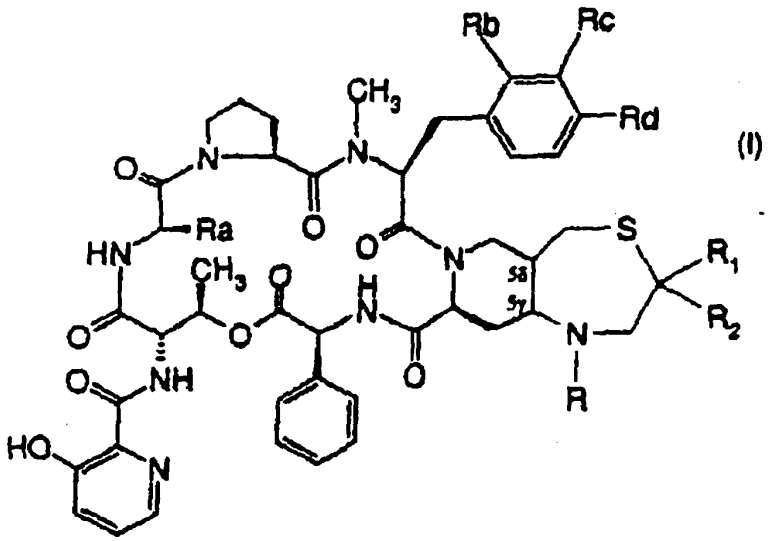
as well as its salts when they exist.

These derivatives are particularly advantageous as antimicrobial agents, optionally combined with at least one group A streptogramin derivative.


Rb
Rc
Rd
CH3
N
O
Ra
HN
CH3
O
NH
HO
N
S
R1
R2
R
(I)

STREPTOGRAMIN DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

The present invention relates to group B streptogramin derivatives of general formula:



(I)

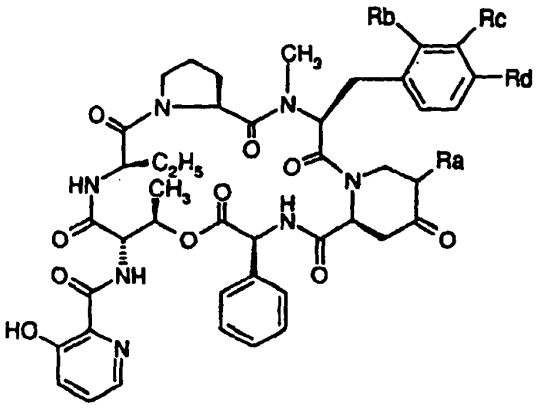
as well as their salts when they exist, which exhibit a particularly advantageous antibacterial activity, alone or combined with a group A streptogramin derivative.

Among the known streptogramins, pristinamycin (RP 7293), an antibacterial of natural origin produced by *Streptomyces pristinaespiralis* was first isolated in 1955. The pristinamycin marketed under the name Pyostacine® consists mainly of pristinamycin I_A combined with pristinamycin II_A.

Another antibacterial of the class of streptogramins: virginiamycin, has been isolated from *Streptomyces virginiae*, ATCC 13161 [Antibiotics and

Chemotherapy, 5, 632 (1955)]. Virginiamycin (Staphylomycine®) consists mainly of factor S combined with factor M_1.

Semisynthetic derivatives of streptogramins represented by the structure:



(A)

in which,

Ra is a radical of structure $-CH_2R'a$ for which R'a is a radical of the heterocyclylthio type which may be substituted or represents a radical of structure =CHR'a for which R'a is a substituted alkylamino, alkyloxy or alkylthio radical, or a radical of the heterocyclylamino, heterocyclyloxy or heterocyclylthio type which may be substituted, Rb and Rc are hydrogen atoms and Rd is a hydrogen atom or a dimethylamino radical, or Ra is a hydrogen atom and Rb is hydrogen or methyl, Rc and Rd are hydrogen or various substituents, have been described in patents or patent applications EP 133097, EP 248703, EP 770132 and EP 772630.

Combined with a semisynthetic component of the group A streptogramins, they manifest a synergy of action and

can be used as antibacterial agents either by the injectable route alone, or only by the oral route.

It has now been found, and this is what constitutes the subject of the present invention, that the products of general formula (I) in which:

R represents a hydrogen atom or an alkyl radical of structure R'-CH_2-(R' being a straight or branched alkyl) or an acyl radical optionally substituted with hydroxyl, R_1 and R_2, which are identical or different, represent a hydrogen atom or an alkyl radical,

Ra is a methyl or ethyl radical, and

Rb, Rc and Rd have the definitions below:

1) Rb and Rc are hydrogen atoms and Rd is a hydrogen atom or a methylamino or dimethylamino radical

2) Rb is a hydrogen atom, Rc is a hydrogen, chlorine or bromine atom, or represents an alkenyl radical (3 to 5C), and Rd is a radical -NMe-R''' for which R''' represents a radical alkyl, hydroxyalkyl (2 to 4C) or alkenyl (2 to 8C) optionally substituted with phenyl, cycloalkyl(3 to 6C)methyl, benzyl, benzyl substituted [with one or more halogen atoms or hydroxyl, alkyl, alkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino or dialkylamino radicals], heterocyclylmethyl or heterocyclylethyl in which the heterocyclyl portion is saturated or unsaturated and contains 5 to 6 members and 1 or 2 heteroatoms chosen from sulfur, oxygen or nitrogen optionally substituted

[with a radical alkyl, alkenyl (2 to 8 carbons), cycloalkyl (3 to 6 carbons), saturated or unsaturated heterocyclyl (4 to 6 members), phenyl, phenyl substituted as defined above for the definition of R_1 or benzyl] or R''' represents a cyanomethyl or carboxymethyl radical, or represents -CORe or $-CH_2CORe$ for which either Re is -OR'e, R'e being alkyl (1 to 6 carbons), alkenyl (2 to 6 carbons), benzyl or heterocyclylmethyl in which the heterocyclyl portion contains 5 to 6 members and 1 or 2 heteroatoms chosen from sulfur, oxygen or nitrogen or Re is a radical alkylamino, alkylmethylamino, heterocyclylamino or heterocyclylmethylamino in which the heterocyclyl portion is saturated and contains 5 to 6 members and 1 or 2 heteroatoms chosen from sulfur, oxygen or nitrogen optionally substituted with an alkyl, benzyl or alkyloxycarbonyl radical,

3) Rb is a hydrogen atom, Rd is a radical $-NHCH_3$ or $-N(CH_3)_2$ and Rc is a chlorine or bromine atom, or represents an alkenyl radical (3 to 5C), [if Rd is $-N(CH_3)_2$],

4) Rb and Rd are hydrogen atoms and Rc is a halogen atom, or an alkylamino or dialkylamino, alkyloxy, trifluoromethoxy, thioalkyl, alkyl (1 to 6C) or trihalomethyl radical,

5) Rb and Rc are hydrogen atoms and Rd is a halogen atom, or an ethylamino, diethylamino or

methylethylamino, alkyloxy or trifluoromethoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl (1 to 6C), phenyl or trihalomethyl radical,

6) Rb is a hydrogen atom and Rc is a halogen atom or an alkylamino or dialkylamino, alkyloxy or trifluoromethoxy, thioalkyl, or alkyl (1 to 3C) radical, and Rd is a halogen atom or an amino, alkylamino or dialkylamino, alkyloxy or trifluoromethoxy, thioalkyl, alkyl (1 to 6C) or trihalomethyl radical

7) Rc is a hydrogen atom and Rb and Rd represent a methyl radical,

manifest particularly advantageous activities, both by the oral and parenteral routes.

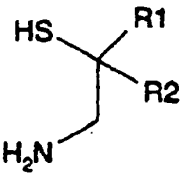
The streptogramin derivatives of general formula (I) are indeed particularly advantageous because of their potent activity both by the oral and parenteral routes, which offers them an undeniable advantage in the case in particular of treatments of serious infections, in a hospital environment by the injectable route, followed by an ambulatory treatment by the oral route which is easier to administer to patients. Thus, the practitioner is no longer obliged to change the class of the medicament for the patient between the end of the hospital treatment and the overall end of the treatment.

In general formula (I) above, the halogen atoms may be chosen from fluorine, chlorine, bromine or

iodine; the alkyl or acyl radicals are straight or branched and, unless otherwise stated, contain 1 to 4 carbon atoms.

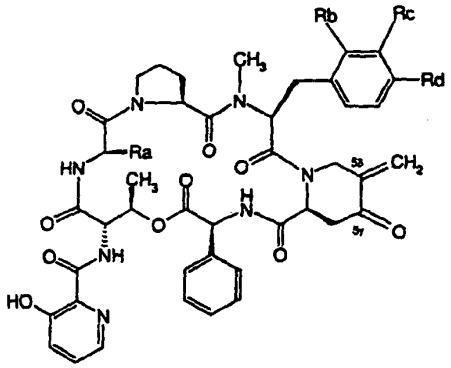
Moreover, the stereochemistry of the ring in 5γ,5δ may be 5γ(R),5δ(S) or 5γ(S),5δ(R). It is understood that the products of the 5γ(R),5δ(S) and 5γ(S),5δ(R) forms as well as their mixtures will fall within the scope of the present invention.

According to the invention, the products of general formula (I) may be prepared by reacting an aminomercaptan of general formula:



(II)

in which R_1 and R_2 are as defined above, with the group B synergistin derivative of general formula:



(III)

in which Ra, Rb, Rc and Rd are as defined above, followed by a treatment for reducing the 5δ-aminoethylthiomethyl derivative obtained, and then optionally the separation of the stereoiosmers and/or

of the substitution of the hexahydrothiazepino ring with a radical R as defined above.

The addition of the aminomercaptan of general formula (II) is carried out in an organic solvent such as an alcohol (for example methanol) or a chlorinated solvent (for example dichloromethane, dichloroethane or chloroform) or in a mixture of such solvents, at a temperature of between -30 and 60°C. Preferably, the procedure is carried out in an inert medium (for example under nitrogen or under argon).

The reducing step is carried out according to the usual methods which do not adversely modify the rest of the molecule. In particular, the procedure is carried out in the presence of a hydride (for example an alkali metal borohydride such as sodium borohydride, or for example an alkali metal cyanoborohydride such as sodium cyanoborohydride), in an organic solvent such as a nitrile (for example acetonitrile) in an acetic medium, at a temperature of between -20 and 60°C. Preferably, the procedure is carried out in an inert medium (for example under nitrogen or under argon).

When R is an alkyl radical as defined above, the substitution with a radical R is carried out by treatment in a reducing medium, with an aldehyde of general formula:

R-CHO (IV)

in which R is as defined above.

The procedure is carried out in an organic solvent such as a nitrile (for example acetonitrile) in an acetic medium, at a temperature of between -20 and 60°C. The reducing conditions are used by any method which does not adversely modify the rest of the molecule, in particular in the presence of a hydride (an alkali metal borohydride: for example sodium borohydride, an alkali metal cyanoborohydride: for example sodium cyanoborohydride). Preferably, the procedure is carried out in an inert medium (for example under nitrogen or under argon).

When R is an acyl radical, the substitution with a radical R is carried out by acylation of the derivative obtained. The acylation is carried out by any known method which does not adversely modify the rest of the molecule. In particular by treatment with a reactive derivative of an acid such as acid chloride or a reactive ester under the usual conditions for addition of an acid derivative to an amine. In particular in the presence of a tertiary amine (for example triethylamine) or of a condensing agent (for example carbodiimide) at a temperature of between 0 and 60°C, in an organic solvent such as a chlorinated solvent (for example chloroform or dichloromethane), an amide (for example dimethylformamide or N-methylpyrrolidone) or an ether (for example tetrahydrofuran).

When it is desired to obtain a product for which the acyl radical is substituted with a hydroxyl radical, it is preferable to cause an acid derivative whose hydroxyl function has been previously protected to react, or to cause the corresponding halogenated derivative to react and then to hydroxylate the halogenated derivative obtained.

The protection of the hydroxyl radical is carried out by any protective radical whose introduction and removal does not adversely modify the rest of the molecule. In particular according to T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd ed.), A. Wiley - Interscience Publication (1991).

The stereoisomers are separated according to the usual methods, for example by chromatography or by crystallization.

The streptogramin derivative of general formula (III) may be prepared according to the methods described in European Patents EP 133098 and EP 432029, or by analogy with these methods or the methods described in EP 248703, EP 770132, EP 772630 or EP 821697 or described below in the examples.

The streptogramin derivatives of general formula (I) may be purified, where appropriate, by physical methods such as crystallization or chromatography.

Some of the streptogramin derivatives of general formula (I) may be converted to the state of addition salts with acids, by known methods. It is understood that these salts, when they exist, are also included within the scope of the present invention.

As examples of addition salts with pharmaceutically acceptable acids, there may be mentioned the salts formed with inorganic acids (hydrochlorides, hydrobromides, sulfates, nitrates, phosphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulfonates, ethanesulfonates, phenylsulfonates, p-toluenesulfonates, isethionates, naphthylsulfonates or camphorsulfonates, or with substitution derivatives of these compounds).

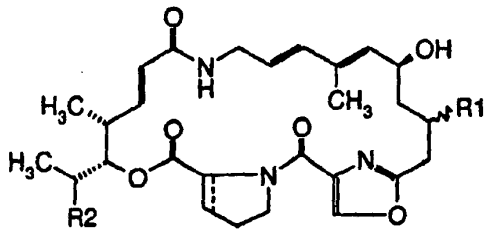
Where appropriate, the derivatives carrying a carboxyl substituent may be converted to metal salts or to addition salts with nitrogenous bases according to methods known per se. These salts may be obtained by the action of a metal (for example alkali or alkaline-earth metal) base, ammonia or an amine, on a product according to the invention, in an appropriate solvent such as an alcohol, an ether or water, or by exchange reaction with a salt of an organic acid. The salt formed precipitates after optional concentration of the solution, it is separated by filtration, decantation or lyophilization. As examples of pharmaceutically acceptable salts, there may be mentioned the salts with

alkali metals (sodium, potassium, lithium) or with alkaline-earth metals (magnesium, calcium), the salt of ammonium, the salts of nitrogenous bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, NN-dimethylethanolamine, benzylamine, dicyclohexylamine, N-benzyl-β-phenethylamine, NN'-dibenzylethylenediamine, diphenylenediamine, benzhydrylamine, quinine, choline, arginine, lysine, leucine, dibenzylamine).

The streptogramin derivatives according to the present invention have antibacterial properties and properties synergizing the antibacterial activity of the group A streptogramin derivatives. They are particularly advantageous because of their activity, alone or combined with components of the group A streptogramins and in particular because of their activity both by the oral and parenteral routes, which opens the way for an ambulatory follow-up treatment without modifying the nature of the medicament.

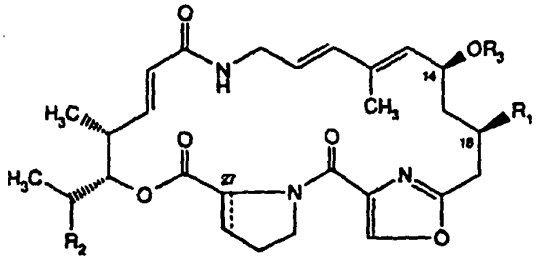
When they are combined with a component or a derivative of the group A streptogramins, they may in particular be chosen, depending on whether it is desired to obtain an orally or parenterally administerable form, from the natural components: pristinamycin II_A, pristinamycin II_B, pristinamycin II_C, pristinamycin II_D, pristinamycin II_E, pristinamycin II_F, pristinamycin II_G or from semisynthetic derivatives as described in patents or patent applications

US 4 590 004 and EP 191662 or from the semisynthetic derivatives of general formula:



(α)

in which R_1 is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl, cycloalkyl, allyl, propargyl, benzyl, or -OR''' radical, R''' being a hydrogen atom, an alkyl, cycloalkyl, allyl, propargyl or benzyl radical, or $-NR_3R_4$, it being possible for R_3 and R_4 to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulfur, R_2 is a hydrogen atom or a methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts. The group A derivatives which may be combined with them may also be chosen from semisynthetic derivatives of general formula:



(β)

in which R_1 represents a halogen atom or an azido or thiocyanato radical, R_2 represents a hydrogen atom or a methyl or ethyl radical, R_3 represents a hydrogen atom, or the residue of an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclylaliphatic ester which may be substituted, and the bond --- represents a single bond (stereochemistry 27R) or a double bond, and their salts when they exist. And in particular, the products of general formula (β) for which the ester residue R_3 may be chosen from: from R'_3-CO- radicals for which R'_3 is phenyl or phenylalkyl which are not substituted or which are substituted on the phenyl radical [with one or more radicals chosen from alkyl, optionally carrying a radical NR''R''' in which the radicals R'' and R''', which are identical or different, may be hydrogen atoms or alkyl radicals which may form together with the nitrogen atom to which they are attached a 3- to 8-membered saturated or unsaturated heterocyclyl radical, optionally comprising another heteroatom chosen from oxygen, sulfur or nitrogen, it being possible for said heterocycle itself to be substituted with one or more radicals (alkyl, hydroxyalkyl, alkyloxyalkyl, alkyloxycarbonylalkyl, aryl, saturated or unsaturated 3- to 8-membered heterocyclyl or heterocyclylalkyl or $-CH_2$-CO-NR''R''') or R'' and/or R''' may be a radical hydroxyalkyl, phenyl, saturated or unsaturated 3- to 8-membered heterocyclylalkyl, -CO-NR''R''' for which

NR''R''' is as defined above, or alkyl or acyl substituted with NR''R''' as defined above] or R'_3 may be chosen from phenyl or phenylalkyl radicals substituted on the phenyl radical with one or more radicals [chosen from alkyl, which may be substituted with an alkyloxy or alkylthio radical themselves optionally carrying a carboxyl radical or a radical NR''R''' as defined above, or chosen from acyloxy which may be substituted with NR''R''' as defined above], or R'_3 may be chosen from alkyl or cycloalkyl radicals optionally substituted [with a carboxyl or carboxyalkyldisulfanyl radical or with a radical NR''R''', $-CH_2$-NR''R''', -CO-NR''R''', or with an alkyloxycarbonyl, alkyloxy or alkyldisulfanyl radical optionally substituted with NR''R''' or -CO-NR''R''' for which NR''R''' is as defined above] or R'_3 may be chosen from saturated or unsaturated 3- to 8-membered heterocyclyl radicals optionally substituted [with alkyl or acyl which are themselves optionally substituted with NR''R'''].

It is understood that the combinations of the derivatives according to the invention and the group A streptogramins are also included within the scope of the present invention.

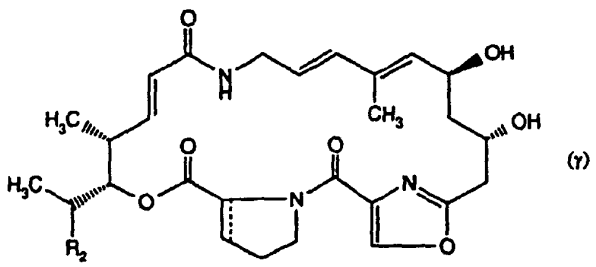
In vitro on *Staphylococcus aureus* 209P, the streptogramin derivatives according to the invention have proved active at concentrations of between 0.12 and 32 μg/ml when combined with a group A streptogramin

derivative such as pristinamycin II_B and at concentrations of between 0.5 and 32 μg/ml on *Staphylococcus aureus* Schiclia (resistant to meticillin) when combined with pristinamycin II_B; in vivo, they synergize the antimicrobial activity of pristinamycin II_B on experimental infections of mice with *Staphylococcus aureus* IP8203 at doses of between 25 and 150 mg/kg subcutaneously or orally (CD_{50}) [30/70 combinations].

Finally, the products according to the invention are particularly advantageous because of their low toxicity. None of the products manifested toxicity at the dose of 150 mg/kg administered twice with a 5-hour interval by the oral route.

The streptogramin derivatives of general formula (α) are described in international application WO 99/05165.

The streptogramin derivatives of general formula (β) which are described in patent application FR 99 08375 are prepared by halogenation, by conversion to an azide or by conversion to a thiocyanate, of a streptogramin derivative of general formula:



(γ)

in which R_2 is as defined above, the bond --- represents a single bond (27R stereochemistry) or a double bond, and whose hydroxyl function at the 14-position has been protected beforehand, followed by the elimination of the protecting radical and, where appropriate, in order to obtain a derivative (β) for which R_3 is other than the hydrogen atom, by introduction of the aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclylaliphatic ester residue which may be substituted (R_3) according to the usual methods which do not adversely modify the rest of the molecule.

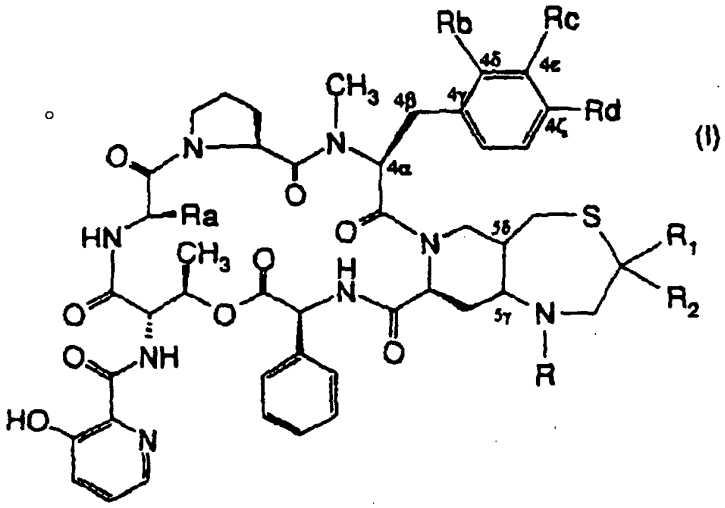
The reactions for halogenation, conversion to an azide or conversion to a thiocyanate may be carried out in the presence of an aminosulfur trifluoride (diethylaminosulfur trifluoride, bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor®), morpholinosulfur trifluoride) or alternatively in the presence of sulfur tetrafluoride, by means of a reagent such as a halide, an azide or a thiocyanate of tetraalkylammonium (tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium), of trialkylbenzylammonium or of trialkylphenylammonium or by means of a halide, an azide or a thiocyanate of an alkali metal optionally supplemented with a crown ether. The reaction is carried out in a chlorinated organic solvent (dichoromethane, dichloroethane, chloroform) or in an ether (tetrahydrofuran) between -78 and 40°C,

preferably under argon or under nitrogen. The use of the hydroxyl derivative of (16S) configuration leads to the derivative of (16R) configuration. The protection and deprotection of the hydroxyl radical at the 14-position is carried out according to the usual methods which do not affect the rest of the molecule [T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (2^{nd} ed.), A. Wiley - Interscience Publication (1991)].

To prepare a product (β) for which R_3 is an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclylaliphatic ester which may be substituted, the esterification is carried out by the reaction of the acid or of a reactive derivative of the acid (acid chloride, reactive ester, anhydride), in the presence or otherwise of a coupling agent (carbodiimide: dicyclohexylcarbodiimide) and of a tertiary amine (trialkylamine: triethylamine, diisopropylethylamine, pyridine or a derivative) and optionally a catalyst such as 4-N-dimethylaminopyridine, at a temperature of between -40 and +80°C in an organic solvent such as an amide (for example dimethylformamide or N-methyl-2-pyrrolidinone), pyridine, a halogenated solvent (for example dichloromethane, dichloroethane or chloroform) or an ether (tetrahydrofuran, dioxane, dimethoxyethane). The functions which can interfere with the reaction are protected beforehand.

The following examples, given without limitation, illustrate the present invention.

In the examples which follow, the NMR spectra were studied in deuterochloroform, the nomenclature used is that of J.O. Anteunis et al., Eur. Biochem., 58, 259 (1975) and in particular:



(I)

The purifications are carried out, by flash chromatography using a 0.063-0.04 mm silica. As the chromatography progresses, the fractions are analyzed by thin-layer chromatography (TLC) on Merck 60F254 silica plates. The fractions corresponding to the same Rf are grouped together and then concentrated to dryness under reduced pressure (30-45°C; 2.7 kPa). The products thus obtained are analyzed by the usual spectroscopic techniques (NMR; IR; MS), which makes it possible to identify the expected products.

EXAMPLE 1

5γ(S),5δ(R)-[5γa,5δb]1,4-Hexahydrothiazepinopristinamycin I_E

4 Å molecular sieve is added, under a nitrogen atmosphere, to 65 g of crude 5δ-(2-aminoethyl)thiomethylpristinamycin I_A in solution in a mixture of 1500 cm^3 of acetonitrile and 150 cm^3 of acetic acid. After stirring for 30 minutes at about 20°C, 5.2 g of sodium cyanoborohydride are added. The stirring is continued for 18 hours. The reaction mixture is then filtered on Clarcel®, rinsed with acetonitrile and then the filtrate is concentrated to dryness under reduced pressure (2.7 kPa), at 30°C, to give a yellow oil which is taken up in 1000 cm^3 of ethyl acetate and 1000 cm^3 of distilled water. The mixture obtained is brought to pH 2 by addition, with stirring, of concentrated hydrochloric acid and is then transferred to a separating funnel. The aqueous phase is separated after settling out and the organic phase is extracted with 200 cm^3 of a 0.1N aqueous solution of hydrochloric acid. The aqueous phases are combined, washed again with 500 cm^3 of ethyl acetate, placed in a round-bottomed flask, with stirring, and then alkalinized to pH 7 by addition of sodium bicarbonate powder. The pH is then adjusted to 8 by addition of concentrated sodium hydroxide and the aqueous phase extracted with twice 600 cm^3 of dichloromethane. The organic phase is decanted off, washed with 200 cm^3 of

distilled water, dried over magnesium sulfate, filtered and concentrated to dryness to give a solid which is stirred in 500 cm^3 of diethyl ether and then filtered to give 57.8 g of a pale yellow powder. 30 g of this solid are purified by flash chromatography (eluent dichloromethane-methanol 98-2 by volume), to give 8.2 g of a solid which is stirred for 1 hour in a mixture of 160 cm^3 of ethyl acetate and diethyl ether (50-50 by volume) and 160 cm^3 of 0.5N hydrochloric acid. The pH of this mixture is adjusted to 3-4 by addition of concentrated sodium hydroxide. The mixture obtained is separated after settling out in a funnel. The aqueous phase is washed with a mixture of ethyl acetate and diethyl ether (50-50 by volume) and then alkalinized to pH 8 by addition of sodium bicarbonate powder and extracted twice with ethyl acetate. The organic phases are combined, washed with water, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C to give 7.2 g of a light yellow solid which is stirred in 500 cm^3 of diethyl ether for 18 hours, filtered, rinsed twice with diethyl ether and then dried at 20°C. 6.6 g of 5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are thus obtained in the form of a white powder melting at 212°C.

^1H NMR spectrum, 400 MHz, $CDCl_3$

0.95 (m, 4H, CH_3 at position 2γ and 5β); 1.3-1.45 (m, 5H, CH_3 at position 1γ, 3γ and 3β); 1.6-1.9 (m, 4H, 2×2β,

3γ and 5δ); 2.05 (m, 1H, 3β); 2.35-2.90 (m, 7H, 2X CH_2S of the 1,4-hexahydrothiazepine ring, 5β, 5ε); 3 (s, 6H, $N(Me)_2$); 3.05-3.20 (m, 6H, 2X4β, NMe and 1H of the 1,4-hexahydrothiazepine ring); 3.30 (broad m, J at mid height = 11 Hz, 1H, 5γ); 3.45 (m, 2H, 3δ, and 1H of the CH_2N of the 1,4-hexahydrothiazepine ring); 3.5 (m, 1H, 3δ); 4.25 (broad d, J = 15 Hz, 1H, 5ε); 4.6 (dd, J = 8 and 6 Hz, 1H, 3α); 4.8 (m, 1H, 2α); 4.9 (m, 2H, 1α and 5α); 5.35 (t, 1H, 4α); 5.6 (d, J = 8 Hz, 1H, 6α); 5.9 (m, 1H, 1β); 6.62 (d, J = 8 Hz, 2H, 4ε); 6.68 (d, J = 9 Hz, 1H, 2NH); 6.96 (d, J = 8 Hz, 2H, 4δ); 7.2-7.4 (m, 7H, $1'H_4$, $1'H_5$ and aromatics at position 6); 7.82 (dd, J = 5 and 2 Hz, 1H, $1'H_6$); 8.52 (m, 2H, 1NH and 6NH); 11.7 (s, 1H, OH).

Crude 5δ-(2-aminoethyl)thiomethylpristinamycin I_A may be obtained in the following manner.

1.58 g of 2-aminoethanethiol are added, under a nitrogen atmosphere, to 12 g of 5δ-methylenepristinamycin I_A in solution in a mixture of 60 cm^3 of dichloromethane and 20 cm^3 of methanol. After 1.5 hours at 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa), at 30°C. The residue obtained is stirred for 3 hours at 20°C in 60 cm^3 of distilled water. The suspension obtained is filtered on sintered glass. The solid obtained is washed with distilled water and then 3 times with diethyl ether. After drying in a desiccator at 45°C, 10.1 g of crude 5δ-(2-aminoethyl)thiomethylpristinamycin

I_A are obtained in the form of a pale yellow powder which is used as it is.

EXAMPLE 2

5γ(R),5δ(S)-[5γa,5δb]1,4-Hexahydrothiazepinopristinamycin I_E

9 g of crude 5δ-(2-aminoethylthio)methyl-pristinamycin I_A are dissolved in 300 cm^3 of acetonitrile at 50°C. After cooling, 30 cm^3 of acetic acid and then 730 mg of sodium cyanoborohydride are added, with stirring. After stirring for 52 hours, the solvent is evaporated under reduced pressure (2.7 kPa at 30°C). The thick oil obtained is taken up in 150 cm^3 of ethyl acetate and 80 cm^3 of distilled water. The mixture obtained is stirred at 20°C and then supplemented with with concentrated sodium hydroxide to a pH of 7-8. After stirring for 15 minutes, the mixture is transferred to a separating funnel. The aqueous phase is separated after settling out and the organic phase is washed twice with 30 cm^3 of distilled water supplemented with sodium chloride. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness (2.7 kPa at 30°C) to give 9 g of a solid which is stirred in 180 cm^3 of isopropyl ether for 2 hours. The solid obtained is filtered, washed with diethyl ether and then dried to give 7.5 g of a pale yellow powder which is purified by flash chromatography (eluent dichloromethane-methanol 95-5 by volume). 2.1 g of 5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydro-thiazepinopristinamycin I_E which is identical to the

product described in Example 1 and 1.4 g of impure 5γ(R),5δ(S)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are thus obtained. The latter is taken up in 30 cm^3 of diethyl ether, stirred overnight, filtered and then dried at 20°C before being purified again by flash chromatography (eluent dichloromethane-methanol 97-3 by volume) to give 360 mg of 5γ(R),5δ(S)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E, in the form of a pale yellow powder melting at 260°C.

^1H NMR spectrum, 400 MHz, $CDCl_3$

1 (t, 3H, CH_3 at position 2γ); 1.14 (ddd, J = 17, 12 and 5 Hz, 1H, 5β), 1.35 (m, 4H, CH_3 at position 1γ and 3β); 1.5 (m, 1H, 3γ); 1.65-1.75 (m, 2H, 2β); 2.05 (m, 1H, 3β); 2.34 (broad dd, J = 17 and 4 Hz, 5β); 2.5 (m, 2H, CH_2S of the 1,4-hexahydrothiazepine ring and 5δ); 2.75 (m, 3H, 2H of the 1,4-hexahydrothiazepine ring and 5ε); 2.9-3.1 (m, 13H, $N(CH_3)_2$, NMe, 4β and 3H of the 1,4-hexahydrothiazepine ring); 3.22 (m, 2H, 4β and CH_2N of the 1,4-hexahydrothiazepine ring); 3.4-3.60 (m, 3H, 3δ and 5γ); 4.6 (m, 2H, 3α and 5ε); 4.7 (m, 1H, 2α); 4.90 (dd, J = 10 and 1.5 Hz, 1H, 1α); 5.10 (broad singlet, 1H, 5α); 5.52 (dd, J = 10 and 8 Hz, 1H, 4α); 5.64 (d, J = 8 Hz, 1H, 6α); 5.9 (m, 1H, 1β); 6.53 (d, J = 8 Hz, 2H, 4δ); 6.72 (d, J = 10 Hz, 1H, 2NH); 6.90 (d, J = 8 Hz, 2H, 4ε); 7.08 (dd, J = 8 and 5 Hz, 1H, $1'H_5$); 7.20 (dd, J = 8 and 1.5 Hz, 1H, $1'H_4$); 7.35 (m, 5H, aromatics at position 6); 7.78 (dd, J = 5 and 1.5 Hz,

1H, 1'H_6); 8.52 (d, J = 10 Hz, 1H, 1NH); 8,78 (d, J = 8 Hz, 1H, 6NH); 11.72 (s, 1H, OH).

EXAMPLE 3

4ε-Chloro-5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E

By carrying out the procedure as in Example 1, but starting with 12.7 g of crude 4ε-chloro-5δ-(2-aminoethylthio)methylpristinamycin I_A, molecular sieve, 300 cm^3 of acetonitrile and 30 cm^3 of acetic acid, and addition, after stirring for 2 hours, of 955 mg of sodium cyanoborohydride, an orange-colored solid is obtained after stirring for 18 hours at 20°C, filtering, washing with acetonitrile and concentrating to dryness under reduced pressure (2.7 kPa) at 30°C. The latter is taken up in 300 cm^3 of ethyl acetate and 300 cm^3 of distilled water and then treated as described in Example 1 to give 6.6 g of a pale yellow powder which is purified by flash chromatography (eluent dichloromethane-methanol 98-2 by volume). 1.3 g of impure 4ε-chloro-5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E and 910 mg of impure 4ε-chloro-5γ(R),5δ(S)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are obtained.

The 1.3 g of impure 4ε-chloro-5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are dissolved in 30 cm^3 of a dichloromethane-methanol (85-15 by volume) mixture and then supplemented with 650 mg of silica. The mixture obtained is stirred for 5 hours at

20°C and then filtered. The silica is rinsed with the same eluent and the filtrate concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The solid obtained is stirred in diethyl ether, filtered and then dried to give 1.26 g of a white powder which is purified by flash chromatography (eluent dichloromethane-methanol 98-2 by volume). 810 mg of a solid are thus obtained, which solid is stirred in 20 cm^3 of diethyl ether, filtered and then dried under reduced pressure (30 Pa), at 20°C, to give 610 mg of 4ε-chloro-5γ(S),δ(R)-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E in the form of a white solid melting at 224°C.

^1H NMR spectrum, 400 MHz, $CDCl_3$

0.92 (t, 3H, CH_3 at position 2γ); 1.24 (m, 2H, 3β and 5β); 1.32 (d, 3H, CH_3 at position 1γ); 1.40 (m, 1H, 3γ); 1.55-1.70 (m, 5H, 2×2β, 3γ and 5δ); 1.96 (m, 1H, 3β); 2.36 (dd, J = 10 and 12 Hz, 1H, CH_2S of the 1,4-hexahydrothiazepine ring), 2.5-2.9 (m, 13H, 5β, 5ε, $N(Me)_2$ and 4H of the 1,4-hexahydrothiazepine ring); 2.95-3.20 (m, 5H, 4β and NMe); 3.35 (m, 3H, 3δ, 5γ and 1H of the CH_2N of the 1,4-hexahydrothiazepine ring); 3.5 (m, 1H, 3δ); 4.20 (broad d, J = 15 Hz, 1H, 5ε); 4.52 (dd, J = 8 and 6 Hz, 1H, 3α); 4.78 (m, 1H, 2α); 4.86 (d, J = 10 Hz, 1H, 1α); 5 (broad d, J = 6 Hz, 1H, 5α); 5.40 (dd, J = 8 and 10 Hz, 1H, 4α); 5.56 (d, J = 8 Hz, 1H, 6α); 5.9 (m, 1H, 1β); 6.64 (d, J = 10 Hz, 1H, 2NH); 6.80 (d, J = 8 Hz, 1H, 4ε); 6.84 (broad d, J = 8 Hz,

1H, 4δ); 7.05 (broad s, 1H, 4δ); 7.12 (dd, J = 8 and 5 Hz, 1H, 1'H_5); 7.20 (d, J = 8 Hz, 1H, 1'H_4); 7.30-7.40 (m, 5H, aromatics at position 6); 7.68 (broad d, J = 5 Hz, 1H, 1'H_6); 8.35 (d, J = 10 Hz, 1H, 1NH); 8.50 (d, J = 8 Hz, 1H, 6NH); 11.7 (s, 1H, OH).

4ε-Chloro-5δ-(2-aminoethyl)thiomethyl-pristinamycin I_A may be prepared in the following manner:

Crude 4ε-chloro-5δ-(2-aminoethyl)thiomethyl-pristinamycin I_A may be obtained as described in Example 2, from 11.7 g of 4ε-chloro-5δ-methylenepristinamycin I_A, 1.48 g of 2-aminoethanediol, in a mixture of 60 cm^3 of dichloromethane and 20 cm^3 of methanol, at -20°C for 6 hours and then at 20°C for 18 hours. After treating as in Example 2, a solid is obtained which is stirred in 200 cm^3 of diethyl ether, filtered and dried under reduced pressure (30 Pa), at 20°C, to give 12.7 g of crude 4ε-chloro-5δ-(2-aminoethyl)thiomethylpristinamycin I_A in the form of a pink powder which is used as it is.

4ε-Chloro-5δ-methylenepristinamycin I_A may be obtained in the following manner:

1.9 g of N-chlorosuccinimide are added to 11.4 g of 5δ-methylenepristinamycin I_A in solution in 120 cm^3 of acetonitrile under an argon atmosphere. The mixture is stirred under reflux for 2 hours and then supplemented with 346 mg of additional N-chlorosuccinimide. After refluxing for an additional 1.5 hours and

stirring for 18 hours at 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The solid obtained is stirred for 4 hours in 250 cm^3 of diethyl ether, filtered, rinsed and then dried in a fume cupboard at 20°C to give 11.7 g of 4ε-chloro-5δ-methylenepristinamycin I_A in the form of a pink powder which is used as it is.

EXAMPLE 4

5γ(S),5δ(R)-4-Methyl-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E

1.5 g of 5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E, in solution in 45 cm^3 of acetonitrile, are introduced into a round-bottomed flask, under an argon atmosphere, and then 121 mg of sodium cyanoborohydride, 286 mg of paraformaldehyde and 4.5 cm^3 of acetic acid are added successively. After stirring for 18 hours at 20°C, the mixture is filtered and then concentrated to dryness (2.7 kPa) at 30°C. The solid obtained is taken up, with stirring, in 60 cm^3 of ethyl acetate and 20 cm^3 of distilled water. The mixture is acidified to pH 2 by addition of 15 cm^3 of 1N hydrochloric acid, stirred for 2.5 hours and then transferred to a separating funnel. The aqueous phase is extracted with 15 cm^3 of ethyl acetate. The aqueous phases are combined and brought to pH 7 by slow addition, with stirring, of solid sodium bicarbonate. The pH is adjusted to 8 by addition of 1N sodium hydroxide and the aqueous phase is extracted with twice

50 cm^3 of ethyl acetate. The organic phases are combined, washed with 10 cm^3 of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. 1.2 g of a pale yellow powder are thus obtained, which powder is purified by flash chromatography (eluent dichloromethane-methanol 97-3 by volume) to give a solid which is taken up in diethyl ether, filtered and dried under reduced pressure (30 Pa) at 20°C. 620 mg of 5γ(S),5δ(R)-4-methyl-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E are thus obtained in the form of a pale yellow solid melting at 202°C.

Mass spectrum

DCI (NH_3) m/z = 954, MH^+

EXAMPLE 5

5γ(R),5δ(S)-4-Methyl-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E

By carrying out the procedure as in Example 4, but starting with 410 mg of impure 5γ(R),5δ(S)-[5γa,5δb]1,4-hexahydrothiazepinopristin-amycin I_E in 13 cm^3 of acetonitrile, 33 mg of sodium cyanoborohydride, 78 mg of paraformaldehyde and 1.3 cm^3 of acetic acid, and after stirring for 18 hours at 20°C, 380 mg of a white powder are obtained, which powder is purified by flash chromatography (eluent dichloromethane-methanol 97-3 by volume) to give 230 mg of 5γ(R),5δ(S)-4-methyl-[5γa,5δb]1,4-hexahydro-

thiazepinopristinamycin I_E in the form of a pale yellow powder melting at 200°C.

^1H NMR spectrum, 400 MHz, $CDCl_3$

0.98 (t, 3H, CH_3 at position 2γ); 1.8-1.9 (m, 5H, CH_3 at position 1γ, 3β and 5β); 1.52 (m, 1H, 3γ); 1.65-1.85 (m, 3H, 2β and 3γ); 2.04 (m, 1H, 3β); 2.45-2.60 (m, 6H, NCH_3 and 1H of the CH_2S of the 1,4-hexahydrothiazepine ring, 5β and 5δ), 2.7 (dd, J = 17 and 5 Hz, 1H, 5ε); 2.75-2.95 (m, 4H, 4H of the 1,4-hexahydrothiazepine ring); 2.96 (s, 6H, $N(CH_3)_2$); 3.04-3.28 (m, 7H, 1H of NCH_2 of the 1,4-hexahydrothiazepine ring), 4β, 5γ and NMe); 3.42-3.58 (m, 2H, 3δ); 4.58 (dd, J = 8 and 6 Hz, 1H, 3α); 4.66 (broad doublet, J = 17 Hz, 1H, 5ε); 4.90 (dd, J = 10 and 1.5 Hz, 1H, 1α); 5.18 (broad singlet, 1H, 5α); 5.60 (dd, J = 10 and 8 Hz, 1H, 4α); 5.68 (d, J = 10Hz, 1H, 6α); 5.94 (m, 1H, 1β); 6.54 (d, J = 8 Hz, 2H, 4ε); 6.76 (d, J = 8Hz, 1H, 2NH); 6.92 (d, J = 8Hz, 2H, 4δ); 7.08 (dd, J = 8 and 5 Hz, 1H, $1'H_5$); 7.20 (dd, J = 8 Hz and 1.5 Hz, 1H, $1'H_4$); 7.3-7.4 (m, 5H, aromatics at position 6); 7.78 (dd, J = 5 and 1.5 Hz, 1H, $1'H_6$); 8.56 (d, J = 10 Hz, 1H, 1NH); 8.80 (d, J = 8 Hz, 1H, 6NH); 11.76 (s, 1H, OH).

EXAMPLE 6

5γ(S),5δ(R)-4-Ethyl-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E

By carrying out the procedure as in Example 4, but starting with 1.3 g of impure 5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydrothiazepinopristin-

amycin I_E in 39 cm^3 of acetonitrile, 105 mg of sodium cyanoborohydride, 310 mg of acetaldehyde, and 3.9 cm^3 of acetic acid, and after stirring for 2.5 hours at 20°C, 1.1 g of a pale yellow powder are obtained, which powder is purified by flash chromatography (eluent dichloromethane-methanol 97-3 by volume) to give a solid which is stirred in 16 cm^3 of diethyl ether, filtered and dried under reduced pressure (30 Pa) at 20°C. 690 mg of 5γ(S),5δ(R)-4-ethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are thus obtained in the form of a pale yellow powder melting at 202°C.

Mass spectrum

FAB (NBA matrix) m/z = 968, MH^+

EXAMPLE 7

5γ(S),5δ(R)-2,2-Dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E

5γ(R),5δ(S)-2,2-Dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E

By carrying out the procedure as in Example 1, but starting with 31 g of crude 5δ-[(1-methyl)aminopropyl]thiomethylpristinamycin I_A, 780 cm^3 of acetonitrile, 78 cm^3 of acetic acid, 2.43 g of sodium cyanoborohydride and after stirring for 18 hours at 20°C, 25.65 g of a solid are obtained, after treatment, which solid is purified by flash chromatography (eluent dichloromethane-methanol 98-2 by volume) to give a solid which is dried under reduced pressure (30 Pa) at

20°C. 8.3 g of 5γ(S),5δ(R)-2,2-dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are thus obtained in the form of a pale yellow solid melting at 210°C.

^1H NMR spectrum, 600 MHz, $CDCl_3$

0.90 (ddd, J = 17, 6 and 5 Hz, 1H, 5β); 0.94 (m, 3H, CH_3 at position 2γ); 1.12 (s, 3H, CH_3); 1.28-1.45 (m, 8H, CH_3 at position 1γ, 3β and 3γ); 1.62-1.82 (m, 4H, 2β, 3γ and 5δ); 2 (m, 1H, 3β); 2.38 (broad s, 1H, NH), 2.42 (d, J = 17 Hz, 5β), 2.46 (dd, 1H, 1H of SCH_2 of the 1,4-hexahydrothiazepine ring); 2.55 (m, 3H, 2H of the 1,4-hexahydrothiazepine ring and 5ε); 2.8 (d, 1H, 1H of NCH_2 of the 1,4-hexahydrothiazepine ring), 2.96 (s, 6H, $N(Me)_2$); 3-3.15 (m, 7H, NMe, 5γ and 4β); 3.36 (m, 1H, 3δ); 3.5 (m, 1H, 3δ); 4.2 (broad d, J = 17 Hz, 1H, 5ε); 4.58 (dd, J = 8 and 6 Hz, 1H, 3α); 4.78 (m, 1H, 2α); 4.85 (m, 2H, 1α and 5α); 5.28 (t, 1H, 4α); 5.54 (d, J = 8Hz, 1H, 6α); 5.86 (m, 1H, 1β); 6.60 (d, J = 8 Hz, 2H, 4ε); 6.64 (d, J = 8Hz, 1H, 2NH); 6.94 (d, J = 8Hz, 2H, 4δ); 7.22 (dd, J = 8 and 5 Hz, 1H, 1'H5); 7.27-7.37 (m, 6H, $1'H_4$ and aromatics at position 6); 7.8 (dd, J = 5 and 1.5 Hz, 1H, $1'H_6$); 8.48 (m, 2NH, 6NH, and 1NH); 11.68 (s, 1H, OH).

In the same chromatography, 1.85 g of 5γ(R),5δ(S)-2,2-dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E are isolated in the form of a pale yellow solid melting at 202°C.

^1H NMR spectrum, 600 MHz, $CDCl_3$

0.86 (ddd, J = 17, 12 and 5 Hz, 1H, 5β); 0.95 (t, 3H, CH_3 at position 2γ); 1.15 (s, 3H, CH_3); 1.35 (m, 4H, CH_3 at position 1γ and 3γ); 1.45 (m, 4H, CH_3 at position 3β); 1.6-1.8 (m, 3H, 2β and 3γ); 2.14 (broad dd, J = 17 and 4 Hz, 1H, 5β); 2.2 (d, J = 15 Hz, 1H, 1H of the NCH_2 of the 1,4-hexahydrothiazepine ring); 2.45 (broad s, width at midheight 10Hz, 1H, 5δ); 2.7 (m, 2H, 1H of the CH_2S of the 1,4-hexahydrothiazepine ring and 5ε); 2.9-3 (m, 8H, $N(Me)_2$, 2H of the 1,4-hexahydrothiazepine ring), 3.05 (dd, 1H, 4β); 3.08 (s, 3H, NMe), 3.15 (dd, 1H, 4β); 3.4 (m, 1H, 3δ); 3.52 (m, 2H, 3δ and 5γ); 4.54 (dd, J = 8 and 6 Hz, 1H, 3α); 4.62 (broad d, J = 15 Hz, 1H, 5ε); 4.88 (dd, J = 10 and 1.5 Hz, 1H, 1α); 4.98 (broad s, 1H, 5α); 5.38 (dd, J = 10 and 8Hz, 1H, 4α); 5.62 (d, J = 8 Hz, 1H, 6α); 5.88 (m, 1H, 1β); 6.56 (d, J = 8 Hz, 2H, 4ε); 6.7 (d, J = 8Hz, 1H, 2NH); 6.84 (d, J = 8Hz, 2H, 4δ); 7.15 (dd, J = 8 and 5 Hz, 1H, $1'H_5$); 7.24 (dd, J = 8 and 1.5Hz, 1H, $1'H_4$); 7.28-7.40 (m, 5H, aromatics at position 6); 7.8 (dd, J = 5 and 1.5 Hz, 1H, $1'H_6$); 8.56 (d, J = 10 Hz, 1H, 1NH); 8.76 (d, J = 8Hz, 1H, 6NH); 11.72 (s, 1H, OH).

The crude 5δ-[(1-methyl)aminopropyl]-thiomethylpristinamycin I_A may be obtained as described below by analogy with Example 2.

5.49 g of 1-amino-2-methyl-2-propanethiol hydrochloride and 5.1 cm^3 of triethylamine are added at -30°C, under a nitrogen atmosphere, to 30 g of 5δ-methylenepristinamycin I_A in solution in a mixture of

150 cm^3 of dichloromethane and 45 cm^3 of methanol. After stirring for 7.5 hours at a temperature of -20 to -15°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is taken up in 500 cm^3 of distilled water and 500 cm^3 of dichloromethane. The aqueous phase is separated after settling out and then extracted with 300 cm^3 of dichloromethane. The organic phases are combined, washed successively with 500 cm^3 of distilled water and 200 cm^3 of distilled water saturated with sodium chloride and then dried over magnesium sulfate, filtered and concentrated to dryness, under reduced pressure (2.7 kPa) at 30°C, to give a solid which is stirred in 300 cm^3 of diethyl ether. After filtration, the solid obtained is dried (30 Pa), at 30°C, to give 31.3 g of crude 5δ[(1-methyl)aminopropyl]thiomethyl-pristinamycin I_A in the form of a cream-colored powder which is used as it is.

EXAMPLE 8

5γ(S),5δ(R)-2,2,4-Trimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E

By carrying out the procedure as in Example 4, but starting with 1.5 g of impure 5γ(S),5δ(R)-2,2-dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E in 3 cm^3 of acetonitrile, 118 mg of sodium cyanoborohydride, 278 mg of paraformaldehyde and 0.3 cm^3 of acetic acid, and after stirring for 17.5 hours at 20°C, 1.13 g of a

white powder are obtained, which powder is purified by flash chromatography (eluent dichloromethane-methanol 98-2 by volume) to give 459 mg of 5γ(S),5δ(R)-2,2,4-trimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E in the form of a white powder melting at 220°C.

Mass spectrum

DCI(NH3) m/z = 981, MH^+

EXAMPLE 9

5γ(S),5δ(R)-2,2-Dimethyl-4-(4-hydroxybutyryl)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E

2.85 g of 5γ(S),5δ(R)-2,2-dimethyl-4-(4-bromobutyryl)-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E in solution in 100 cm^3 of dimethylformamide and 0.44 cm^3 of morpholine are introduced into a round-bottomed flask maintained under a nitrogen atmosphere, at 24°C. After stirring for 4.5 hours, the mixture is poured over 1000 cm^3 of distilled water and 500 cm^3 of dichloromethane. The organic phase is decanted off, extracted with twice 500 cm^3 of distilled water and then with 500 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered, concentrated to dryness under reduced pressure (2.7 kPa), at 30°C, to give 2.6g of an oil. This residue is purified by flash chromatography (eluent dichloromethane-methanol 97-3 by volume) to give a solid which is stirred in diethyl ether, filtered and dried under reduced pressure (30 Pa), at 20°C. 140 mg of 5γ(S),5δ(R)-2,2-dimethyl-4-(4-

hydroxybutyryl)-[5γa,5δb]1,4-hexahydrothiazepino-pristinamycin I_E are thus obtained, in the form of a solid melting at 194°C.

Mass spectrum

FAB(NAB matrix) m/z = 1054, MH^+

5γ(S),5δ(R)-2,2-Dimethyl-4-(4-bromobutyryl)-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E may be prepared in the following manner:

2 g of 5γ(S),5δ(R)-2,2-dimethyl-[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E, 80 cm^3 of dichloromethane on amylene and 0.44 cm^3 of triethylamine are introduced into a round-bottomed flask, at -10°C, and then 0.378 cm^3 of 4-bromobutyric acid chloride in solution in 20 cm^3 of dichloromethane on amylene are then added dropwise over 1 hour 10 minutes. After stirring for 22 hours at 20°C, 0.146 cm^3 of triethylamine and 0.126 cm^3 of 4-bromobutyric acid chloride are added at 0°C. The reaction mixture is again stirred for 18 hours, at 20°C, and then poured over 40 cm^3 of distilled water. The mixture obtained is separated after settling out and the organic phase is washed successively with 20 cm^3 of distilled water and 20 cm^3 of water saturated with sodium chloride. The resulting organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa), at 30°C, to give 2.89 g of 5γ(S),5δ(R)-2,2-dimethyl-4-(4-bromobutyryl)-

[5γa,5δb]1,4-hexahydrothiazepinopristinamycin I_E, in the form of an off-white solid which is used in crude form.

The present invention also relates to the pharmaceutical compositions containing at least one streptogramin derivative according to the invention, where appropriate in salt form, in the pure state or in the form of a combination with one or more compatible and pharmaceutically acceptable diluents or adjuvants. The invention also relates to the above pharmaceutical compositions when they contain, in addition, at least one group A streptogramin derivative, or where appropriate one of its salts, combined with the streptogramin(s) of general formula (I).

The compositions according to the invention may be used by the oral, parenteral, topical or rectal route or in the form of aerosols.

As solid compositions for oral administration, tablets, pills, gelatin capsules, powders or granules may be used. In these compositions, the active product according to the invention, generally in the form of a combination, is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose or starch. These compositions may comprise substances other than diluents, for example a lubricant such as magnesium stearate or a coating intended for a controlled release.

As liquid compositions for oral administration, there may be used solutions which are

pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents such as water or paraffin oil. These compositions may also comprise substances other than diluents, for example wetting, sweetening or flavoring products.

Compositions for parenteral administration may be emulsions or sterile solutions. As solvent or vehicle, there may be used propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, for example ethyl oleate. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents.

Sterilization may be carried out in several ways, for example with the aid of a bacteriological filter, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

Compositions for topical administration may be, for example, creams, ointments, lotions or aerosols.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active ingredient, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

The compositions may also be aerosols. For use in the form of liquid aerosols, the compositions may be stable sterile solutions or solid compositions which are dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active ingredient is finely divided and combined with a water-soluble solid diluent or vehicle with a particle size of 30 to 80 μm, for example dextran, mannitol or lactose.

In human therapy, the new streptogramin derivatives according to the invention are particularly useful in the treatment of infections of bacterial origin. The doses depend on the desired effect and the duration of the treatment. The doctor will determine the dosage which he judges to be most appropriate depending on the treatment, depending on the age, weight and degree of infection and other factors specific to the subject to be treated. Generally, the doses are between 1 and 3 g of active product in 2 or 3 doses per day, orally for an adult.

The following example illustrates the composition according to the invention.

EXAMPLE

Tablets containing a dose of 250 mg of active product and having the following composition are prepared according to the usual technique:

- 5γ(S),5δ(R)-[5γa,5δb]1,4-hexahydro-

thiazepinopristinamycin 1_E..... 75 mg

- Pristinamycin II_B..... 175 mg
- Excipient: starch, hydrated silica, dextrin, gelatin, magnesium stearate: qs..... 500 mg